Summary of Panel on the Dominant-Lethal Test

by Verne Ray*

The utility of the dominant-lethal (D-L) assay as a member of a test battery for the detection of environmental mutagens is just beginning to be analyzed. Currently, only a few laboratories have sufficient experience with this assay to permit a critical analysis of its sensitivity and reproducibility. However, it is already quite evident that a number of problems plague the usefulness of the D-L assay; especially those related to ascertaining the significance of marginally positive data and the identification of false or non-reproducible results.

Test reproducibility is still a matter of considerable concern to those analyzing D-L data. Genetic toxicologists are in fair agreement over the necessity of demonstrating a reproducible test result in the same stage of spermatogenesis in a dose-related manner. The important parameters of dead and living implants per pregnant female should both reflect the activity of a true mutagen. Preimplantation losses have been observed in the absence of significant increases in dead implants/pregnant female. Although such findings are important in the overall safety assessment of a given agent, they are not necessarily indicators of mutagenic activity. Therefore, such results might better be analyzed in the context of general reproductive studies. As additional data become available on the number of compounds causing preimplantation losses at specific levels in D-L tests, the contributory effect of excessively high dosage regimens can be assessed.

Statistical models, useful in analyzing D-L data, are now being developed. It is quite clear that until agreement is reached between laboratories on the proper model(s) for use with the D-L assay, conflicting data will result. The need for a transformation to reduce the effect of differing variances which occur in dead and total implants per pregnant female has been identified and agreed to by most investigators using the D-L assay. Currently, there is no overall statistical procedure which has been identified as most useful in the D-L assay. Until the power of various statistical procedures for detecting mutagenic activity have been compared, no single model should be accepted for general use. However, the comparison of test data on a weekly or spermatogenic stage basis with a control regression computed across the entire eight-week period of spermatogenesis appears to satisfy those most actively investigating the utility of the D-L assay.

Dose levels of test substances which are proper for use in mutagenicity studies continue to be debated. It does appear that many investigators agree on protocols employing several levels, the highest of which does not produce toxic effects. The definition of highest dose level used in Segment 2 of the FDA guidelines for reproductive studies can be used as a guide.

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The requirement for an appropriate species of animal with large numbers of offspring and low levels of fetal wastage appears to be satisfied by several random bred and hybrid strains of mice available commercially. However, these strains require constant monitoring to make sure the infectious disease burden does not increase to produce an unacceptable level of fetal wastage. Such increases reduce the sensitivity of the test in the detection of weak mutagens.

New test procedures are being examined for utility in the test battery for mutagenesis. The F_1 translocation test presented in the symposium has the apparent advantage of being more sensitive than the D-L assay and the benefit of being able to analyze the genetic constitution of offspring. However, the duration of the test presents a serious deterrent to rapid screening of compounds at a time when such a requirement is most important. Until more comparative data are available, the D-L assay will probably have the greater utility.

The need of a larger information base for a significant number of chemical classes is most apparent. A number of collaborative mutagenicity studies among industrial, government and private laboratories is urgently needed. Such studies should give baseline data on important classes of compounds and prove the utility of the current procedures in safety evaluation protocols. Standardization of procedures is required before the value of tests such as the D-L can be broadly assessed. Finally, the results of D-L testing should be compared to other procedures such as the cytogenetic and host-mediated assays to provide the necessary supportive data for declaring a substance mutagenic. Factors such as the blood–testicular barrier could markedly affect test results and give false impressions of security. Only after a series of mutagenicity tests have been performed, which attempt to measure the kaleideoscopic array of genetic effects produced by chemicals, can the safety evaluation procedure be considered complete.